Radiation-induced Reactions of Pyridinecarboxylic Esters in Acidic Alcoholic Solutions. Substitution by Alkyl and Hydroxyalkyl Groups and Reduction of Carboxylic Esters to Alcohol[1)]

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The main reactions of pyridinecarboxylic esters induced by Co-60 γ-rays in acidic alcoholic solutions are: 1) substitution on the pyridine ring by alkyl or hydroxyalkyl groups derived from solvent alcohols, and 2) reduction of carboxylic esters to alcohol (hydroxymethyl group). Substitution is dominant in methanol solutions and reduction is dominant in 2-propanol solutions. Carboxylic esters at the 2- and 4-positions are selectively reduced to alcohols. Alkylation results from the attack by hydrogen atoms and hydroxylalkyl radicals. Reduction of carboxylic esters to alcohol is effected by the hydroxyalkyl radicals derived from the radiolysis of alcohols.

Radiation-induced reactions of pyridinecarboxylic acid derivatives including biologically important nicotinamide and nicotinic acid have not yet been thoroughly investigated at least on the basis of product analysis. Schachinger and Heindle reported the radiation-induced hydroxylation for the model compounds of NAD (nicotinamide adenine dinucleotide) in aqueous solutions.[2)] Swallow suggested the formation of a "dimer" during the X-ray irradiation of certain model compounds for NAD.[3)] By means of pulse radiolysis technique, intermediates formed by the reaction of pyridinecarboxylic acid derivatives with reactive species from the radiolysis of water and with the hydroxyalkyl radicals formed during the irradiation of aqueous alcohol have been investigated.[4,5)]

The radiation-induced reactions of esters of 2-, 3-, and 4-pyridinecarboxylic acids and of 2,5-pyridinedicarboxylic acid have been studied and compared with the work of Minisci *et al.* on the free radical substitution,[6)] and our work on the photochemical reactions.[7)]

Experimental

Materials. 2-Pyridinecarboxylic esters were synthesized by the reaction of acid chloride prepared from 2-pyridinecarboxylic acid (GR grade reagent of Tokyo Kasei Co.) with alcohols. The esters were purified by means of vacuum distillation and finally by preparative TLC before use. Commercial methyl and ethyl esters of 3- and 4-pyridinecarboxylic acid (GR grade reagent of Tokyo Kasei Co.) were purified by vacuum distillation. Dimethyl 2,5-pyridinedicarboxylate prepared by the esterification of 2,5-pyridinedicarboxylic acid (GR grade reagent of Tokyo Kasei Co.) in the presence of hydrogen chloride was used after recrystallization from methanol (mp 158 °C).

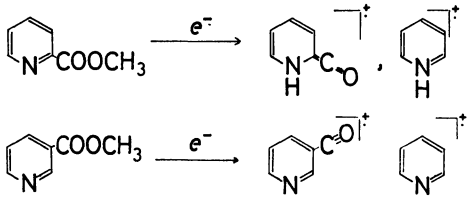
Gamma-irradiation. Solutions containing 0.03 mol dm^{-3} of pyridinecarboxylic esters and 0.05 mol dm^{-3} of sulfuric acid were deaerated by bubbling nitrogen gas for 20 min before irradiation. The solutions were irradiated with the Co-60 γ-irradiation facility of Japan Atomic Energy Research Institute in Takasaki. The normal dose rate and dose were 5×10^5 rad h^{-1} and 1.0×10^7 rad, respectively.

Isolation of Products. The irradiated solutions (each *ca.* 100 cm^3) were concentrated under reduced pressure to about 3 cm^3. After the neutralization with aqueous sodium hydrogencarbonate or sodium carbonate solutions, the products were extracted 7 times each with 5 cm^3 of dichloromethane. The extract was dried over anhydrous sodium sulfate. After concentrating the solution, the products were separated by means of TLC. Except for the methylated products of methyl 3-pyridinecarboxylate, products were obtained in pure form.

Identification of Products. Reduction Products: The identification of 2- and 4-hydroxymethylpyridine was carried out by the comparison of their NMR and IR spectra with those of authentic ones.

Methyl 6-hydroxymethyl-3-pyridinecarboxylate from dimethyl 2,5-pyridinedicarboxylate was identified from the following basis. IR (KBr disc) 3350 (OH), 1725 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ=9.26 (1H, d, J=2.1 Hz, H at 2-position), 8.38 (1H, dd, J=8.0 and 2.1 Hz, H at 4-position), 7.46 (1H, d, J=8.0 Hz, H at 5-position), 4.90 (2H, s, $C\underline{H}_2$-OH), 4.02 (3H, s, $C\underline{H}_3OCO$-); MS (70 V) *m/e* (relative intensity) 167 (77), 166 (100), 138 (57), 137 (23), 136 (36), 108 (15), 106 (11), 79 (35), 78 (45), 59 (11), 53 (12), 52 (15), 51 (30), and 50 (16).

The position of the reduction was confirmed by MS. The difference of the mass-spectrometric behavior between methyl esters at the 2- and 3-positions on the pyridine ring is seen in the following fragmentation patterns.



For the methyl ester of 2-pyridinecarboxylic acid, McLafferty-type fragmentation (intramolecular hydrogen abstraction by the N atom of pyridine) occurs and the peak of $(M-30)^+$ and $(M-58)^+$ are observed, whereas for the methyl ester of 3-pyridinecarboxylic acid the intramolecular hydrogen abstraction cannot occur and the peaks of $(M-31)^+$ and $(M-59)^+$ are observed. This assignment was supported by using methyl-d_3-2-pyridinecarboxylate.

In the mass spectra of the reduction product from dimethyl 2,5-pyridinedicarboxylate, the $(M-59)^+$ peak was observed but the peak of $(M-58)^+$ was very low and the peak of $(M-31)^+$ was higher than that of $(M-30)^+$. Peaks of $(M-29)^+$, $(M-30)^+$, and $(M-31)^+$ can be partly ascribed to the decomposition of the hydroxymethyl moiety of the product. This fact indicates that the reduction occurred at the 2-position.

Alkylation Products: Methyl 6-methyl-3-pyridinecarboxylate was identified by comparison with the authentic sample synthesized by the method of Graf.[8]

Methyl esters of 4-methyl-2-pyridinecarboxylic, 6-methyl-3-pyridinecarboxylic and 2-methyl-4-pyridinecarboxylic acids were identified by the accordance of their NMR spectra with those obtained by Deady *et al.*[9] The alkylated products in the reaction in alcohols other than in methanol were identified by the comparison of NMR spectra with the corresponding methylated products from the reaction of methyl esters in methanol solutions.

The structures of methyl 4,6-dimethyl-2-pyridinecarboxylate which was obtained only in a small amount and methyl 4,6-dimethyl-3-pyridinecarboxylate which was obtained only in a mixture was presumed on the basis of NMR spectra.

Methyl 4,6-dimethyl-2-pyridinecarboxylate, NMR ($CDCl_3$) δ=7.75 (1H, s, H at 3-position), 7.12 (1H, s, H at 5-position), 3.98 (3H, s, $C\underline{H}_3OCO$–), 2.60 (3H, s, $C\underline{H}_3$), and 2.38 (3H, s, $C\underline{H}_3$)

Methyl 4,6-dimethyl-3-pyridinecarboxylate, NMR ($CDCl_3$) δ=8.88 (1H, s, H at 2-position), 6.95 (1H, s, H at 5-position), 3.90 (3H, s, $C\underline{H}_3OCO$–), 2.59 (3H, s, $C\underline{H}_3$), and 2.54 (3H, s, $C\underline{H}_3$).

Methyl 2-hydroxymethyl-4-pyridinecarboxylate was identified by the comparison of its spectral data with those obtained by Ninomiya *et al.*[10]

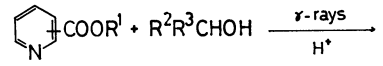
Methyl 6-hydroxymethyl-4-methyl-2-pyridinecarboxylate: mp 27.0—28.5 °C; IR (KBr disc) 3350 (OH) and 1725 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ=7.81 (1H, d, J=1 Hz, H at 3-position), 7.30 (1H, d, J=1 Hz, H at 5-position), 4.79 (2H, s, $HOC\underline{H}_2$–), 3.98 (3H, s, $C\underline{H}_3OCO$–), 2.45 (3H, s, $C\underline{H}_3$–); MS (70 V), *m/e* (relative intensity), 181 (38), 180 (57), 166 (13), 152 (8), 151 (9), 148 (11), 124 (8), 123 (100), 122 (11), 121 (10), 120 (14), 119 (7), 105 (35), 93 (8), 92 (8); Found: C, 60.80; H, 4.87; N, 7.68%; M^+, 181 Calcd for $C_9H_{10}NO_3$: C, 59.94; H, 5.59; N, 7.77%; M, 181.

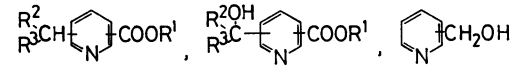
Determination of the Yields of Products. For the determination of the yields of the alkylated and hydroxyalkylated products the gravimetric method after the separation by TLC was applied. The composition of the methylation products from methyl 3-pyridinecarboxylate, which could not be separated by means of TLC was estimated by NMR. For the study of the effect of the acid concentration on the reaction of ethyl 2-pyridinecarboxylate in ethanol, the yields of the products were determined by means of gas-chromatography (column, Carbowax 20M or Triton QS 15; temperature, 160—180 °C). For the determination of the yields of hydroxymethylpyridines, gas-chromatography was employed.

Calculation of the Electronic States. The electronic states of pyridinecarboxylic esters were calculated using the CNDO/2 program (Q.C.P.E. 141) prepared by Pople, Beveridge and Dobosh and arranged by Kihara, Fujikawa, and Aoyama. The structural parameters obtained for 3-pyridinecarboxylic acid[11] was used as a basis. For the other structural parameters, the generally accepted values are substituted, and the structure of the ester group in 3-pyridinecarboxylic ester is assumed for 2- and 4-pyridinecarboxylic esters.

Results and Discussion

The main reactions of pyridinecarboxylic esters in acidic alcoholic solutions under Co-60 γ-irradiation are: 1) the substitution on the pyridine ring by alkyl and/or hydroxyalkyl groups which originate from the solvent alcohols, and 2) the reduction of alkoxycarbonyl group to hydroxymethyl group. Whether reduction or alkylation (or hydroxyalkylation) is predominant depends on the structure of the substrates and on the alcohols used as the solvents.





Alkylation and Hydroxyalkylation. Results on the radiation-induced alkylation and hydroxyalkylation in 2-, 3-, and 4-pyridinecarboxylic esters are summarized in Table 1. Except for 4-pyridinecarboxylic ester, alkyla-

Table 1. Radiation-induced alkylation and hydroxyalkylation of pyridinecarboxylic esters
[Substrate]=0.03 mol dm^{-3}; [H_2SO_4] =0.05 mol dm^{-3}; dose rate, 5×10^5 rad h^{-1}; dose, 10^7 rad.

Substrate	Alcohol	Additive (Concn of additive)	Position and group introduced	*G*-value
Methyl 2-pyridinecarboxylate	MeOH		4-Methyl-	1.29
			4,6-Dimethyl-	0.10
			4-Methyl-6-hydroxymethyl-	0.16
	MeOH	I_2(0.015 mol dm^{-3})	No methylated product	
Ethyl 2-pyridinecarboxylate	EtOH		4-Ethyl-	0.12
			6-Ethyl-	0.01
	EtOH	$FeCl_3$ (0.03 mol dm^{-3})	4-Ethyl-	0.02
Butyl 2-pyridinecarboxylate	*n*-BuOH		4-Butyl-	0.10
			6-Butyl	0.08
Isopropyl 2-pyridinecarboxylate	*i*-PrOH		6-Isopropyl	0.02
Methyl 3-pyridinecarboxylate	MeOH		4-Methyl-	0.21
			6-Methyl-	0.58
			4,6-Dimethyl-	0.31
	MeOH	I_2 (0.015 mol dm^{-3})	No methylated product	
Ethyl 3-pyridinecarboxylate	EtOH		6-Ethyl-	1.42
Methyl 4-pyridinecarboxylate	MeOH		2-Methyl	0.16
			2-Hydroxymethyl	0.23
	MeOH	I_2 (0.015 mol dm^{-3})	No methylated product	

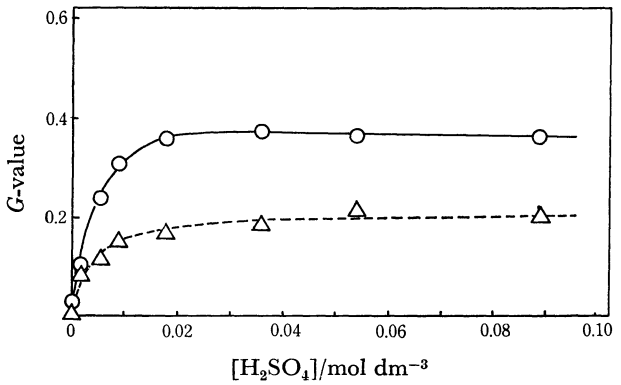
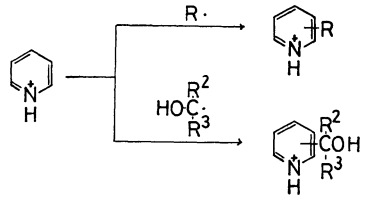


Fig. 1. Effect of the concentration of sulfuric acid on the radiation-induced ethylation and reduction of ethyl 2-pyridinecarboxylate.
-△- Ethyl 4-ethyl-2-pyridinecarboxylate, -○- 2-hydroxymethylpyridine. [Ethyl 2-pyridinecarboxylate] = 0.03 mol dm^{-3}; dose rate, 4×10^5 rad h^{-1}; dose, 8×10^6 rad.

tion is dominant over hydroxyalkylation. Figure 1 shows that the alkylation occurs in an acidic environment where pyridinecarboxylic ester is in the cationic pyridinium form.

The fact that the alkylation is completely inhibited by iodine and iron(III) chloride shows that the reaction proceeds *via* free radical intermediates. However, there is a difference between the radiation-induced reaction and the free radical reaction of pyridine derivatives in alcohol, where hydroxyalkylation is dominant over alkylation.[6] In both cases hydroxyalkyl radicals are expected to play an important role.

Free radical substitution of pyridinium compounds has been investigated by Minisci and his coworkers.[6] According to them, alkyl radicals bring about alkylation and hydroxyalkyl radicals hydroxyalkylation.



Reported *G*-values (radiation-chemical yield) for primary reactive species from the radiolysis of methanol are 2.0 for electron, 1.1 for H·, 0.2 for ·OH, 0.2 for ·CH_3, and 2.7 for ·CH_2OH, respectively.[12] The fact that alkylation is favored over hydroxyalkylation in radiation-induced reactions is not consistent with the higher *G*-value of ·CH_2OH and lower *G*-value of ·CH_3.

The difference between the radiation-induced reaction and the free radical-initiated reaction in alcohol is the participation of hydrogen atoms in the former. (Under the acidic conditions which we employed, electrons should be very effectively converted to hydrogen atoms and the formation of 3.1H· per 100 eV of absorbed radiation energy is expected.) Radiation-induced alkylation can be explained by the initial attack of H

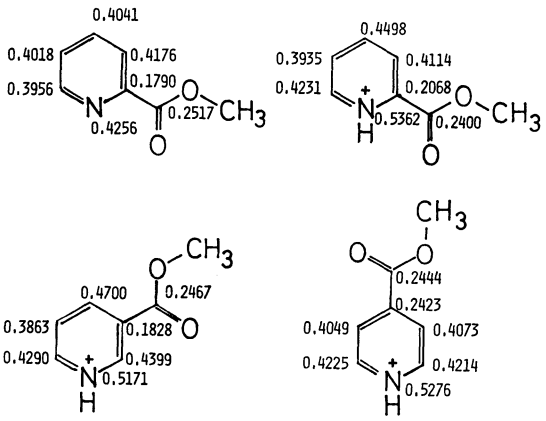
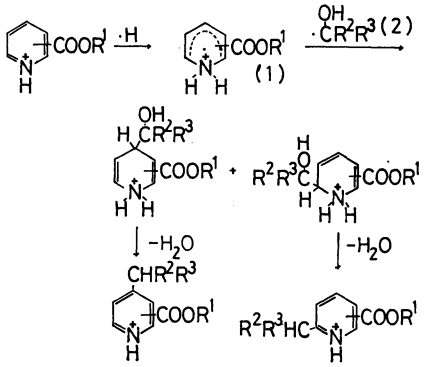


Fig. 2. Free valence in π-electronic systems of pyridine carboxylic esters calculated by CNDO/2.

atoms to the nitrogen atom, which has the greatest free valence among the atoms constituing the pyridine ring (Fig. 2), followed by the attack of hydroxyalkyl radicals and the elimination of water.



As to the alkylation and hydroxyalkylation, the radiation induced reaction is similar to the photoreaction;[13] alkylation is predominant over hydroxyalkylation and the alkylation occurs at α- and γ-position of pyridine nucleus. Photochemically excited pyridinium abstracts a hydrogen atom from alcohol to give the intermediate (**1**) and hydroxyalkyl radical (**2**). This should be the reason of the similarity between the radiation-induced reaction and the photochemical reaction.

Reduction of Carboxylic Ester to Alcohol. The remarkable reaction induced by ionizing radiation is the reduction of the carboxylic ester group to the hydroxymethyl group. In Table 2, *G*-values for the reduction of methyl esters of pyridinecarboxylic acids in several alcohols are summarized.

Among the esters of monocarboxylic acids, 2- and 4-pyridinecarboxylic esters are reduced to alcohols, whereas 3-pyridinecarboxylic ester is not reduced. In dimethyl 2,5-pyridinedicarboxylate, the carboxylic ester at the α-position is selectively reduced. The efficiency of the reduction is higher in the secondary alcohol than in the primary alcohols.

As to the intermediacy of the aldehyde, no conclusion has been made: among the products from methyl 2-pyridinecarboxylate we could not identify 2-pyridinecarbaldehyde and the irradiation of 2-pyridinecarbalde-

Table 2. Dependence of G-values for reduction of alkyl pyridinecarboxylates to hydroxymethylpyridines on alcohol

[Substrate]=0.03 mol dm^{-3}; [H_2SO_4]=0.05 mol dm^{-3}; dose rate, 5×10^5 rad h^{-1}; dose, 10^7 rad.

Substrate	Alcohol	G(Hydroxymethylpyridine)
Methyl 2-pyridinecarboxylate	MeOH	0.012
	EtOH	0.54
	n-PrOH	0.46
	n-BuOH	0.40
	i-PrOH	0.93
Ethyl 3-pyridinecarboxylate	MeOH	0.0
	EtOH	0.0
Ethyl 4-pyridinecarboxylate	EtOH	0.13
Dimethyl 2,5-pyridinedicarboxylate[a)]	MeOH	0.03
	i-PrOH	0.26

a) Reduction product is methyl 6-hydroxymethyl-3-pyridinecarboxylate (the product reduced at 2-position of the substrate).

hyde in 2-propanol gave only small amount of 2-hydroxymethylpyridine.

The reduction is brought about by free radicals produced by ionizing radiation, because the reduction is inhibited by iodine and iron(III) chloride. As is seen in Fig. 1, the reduction occurs in acidic conditions.

As the reducing species, hydroxyalkyl radicals and hydrogen atoms should be taken into consideration. Solvated electrons cannot participate in the reduction, because they should react with H^+ rather than with the substrate.

A small amount of 2-hydroxymethylpyridine was obtained in the sun-light irradiation of methyl 2-pyridinecarboxylate in ethanol in the presence of acetone. In this system, the formation of hydroxymethyl radicals is expected.

Table 3. Pai-electron density and π-bond order of the carbonyl moiety in pyridinecarboxylic esters calculated by CNDO/2

Compound	π-Electron density		π-Bond order
	C	O	
Methyl 2-pyridinecarboxylate (neutral form)	0.8243	1.3043	0.8818
Methyl 2-pyridinecarboxylate (pyridinium form)	0.8576	1.2553	0.8885
Methyl 3-pyridinecarboxylate (pyridinium form)	0.8468	1.2769	0.8885
Methyl 4-pyridinecarboxylate (pyridinium form)	0.8546	1.2419	0.8913

The above fact suggests that the reducing species are hydroxyalkyl radicals. The series of $E_{1/2}$ *vs.* SCE -1.30 V ($(CH_3)_2\dot{C}OH$), -1.18 V (CH_3–$\dot{C}HOH$), and -0.98 V ($\cdot CH_2OH$)[14] correlates well with the G-values for the reduction.

The correlation between the reactivity for the reduction and the electronic state of pyridinecarboxylic esters (Table 3) is not so significant. Among the calculated π-electron densities and π-bond orders, the π-electron densities at O atoms of the carbonyl moiety of the substrates show the correlation to the reactivities.

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13) The photoreactions of pyridinecarboxylic esters consist of alkylation (hydroxyalkylation) and alkoxylation. Whether alkylation or alkoxylation is dominant depends on the structure of the pyridinecarboxylic esters and the reaction conditions. Concerning the alkylation (and hydroxyalkylation), the photoreaction of pyridinecarboxylic esters are similar to radiation-induced reactions. Ref. 7.

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